II. REMARKS

Claims 1-19 and 21 and 23-30 are presently pending in this application. Claims 1-18 have been withdrawn pursuant to a restriction requirement. Claims 19, 21, 23 and 25-30 stand variously rejected under 35 U.S.C. §§ 102 and 103. Claim 24 is free of the prior art of record and is objected to for being dependent from a rejected base claim. The remaining rejections are based on U.S. Patent No. 6,149,919 (hereinafter "Domenighini"). For the reasons set forth herein and the reasons set forth with regard to previously cited references, Domenighini in no way renders the pending claims unpatentable. Reconsideration of the application is requested in view of the following remarks.

Overview of the Invention

The pending claims are drawn to methods of immunizing a vertebrate subject by parenteral administration of a parenteral adjuvant comprising a detoxified LT-R72 or LT-K63 mutant of a an *E. coil* heat labile toxin in combination with at least one antigen. As defined by Applicants on page 7, lines 21-26 of the specification, parenteral administration refers to "introduction into the body outside of the digestive tract, such as by subcutaneous, intramuscular, transcutaneous, intradermal, or intravenous administration. This is to be contrasted with adjuvants that are delivered to a mucosal surface, such as oral, intranasal, vaginal, or rectal." Thus, the present invention provides methods using detoxified LT toxins as parenteral adjuvants.

1449 Forms

Applicants acknowledge with appreciation receipt of the initialed 1449 Forms submitted on (1) May 7, 1998; (2) September 11, 1998; and (3) July 18, 2000.

Rejection Under 35 U.S.C. § 102(e)

Claims 19-21, 23 and 25-27 are rejected under 102(e) as allegedly anticipated by Domenighini. (Final Office Action, paragraph 14). It is maintained that Applicants have argued limitations not found in the claims, namely methods of increasing the immunogenicity of a selected antigen using LT-K63 or LT-R72 as a parenteral adjuvant. As such, it is alleged that Domenighini et al. teach a method of immunizing a host using LT–K63 mutant and an antigen. (See, page 4 of the Final Office Action).

Applicants traverse the rejection and supporting remarks.

Applicants have previously argued that Domenighini does not describe, demonstrate or suggest the use of LT-K63 as a parenteral adjuvant. Among other things, the Examiner has indicated that the features of being a "parenteral" adjuvant and of generating an immune response to an antigen (rather than to LT) are not recited in the claims. This is incorrect. The original preamble made it amply clear that the LT-K63 adjuvant and selected antigen are administered parenterally and that the immunization was with regard to the at least one selected antigen. Nonetheless, in order to advance prosecution, the claims have been amended herein to specify (1) that the claimed methods employ an LT mutant as parenteral adjuvants; and (2) that the claimed methods involve immunizing an animal against at least one selected antigen.

For the reasons previously made of record and reiterated herein, Domenighini does not anticipate the methods as claimed. Indeed, an anticipatory reference must disclose each and every element of the claims. *Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986). The single source cited by the Office must also disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.,* 9 USPQ2d 1913 (Fed. Cir. 1989). Moreover, it is well-settled that in order to constitute an anticipatory reference, the cited document must contain an enabling disclosure. *Chester v. Miller*, 15 USPQ2d 1333, 1336 n.2 (Fed. Cir. 1990); see also, *Scripps Clinic & Research Foundation v. Genentech, Inc.,* 18 USPQ2d 1001, 1011 (Fed.

Cir. 1991). In other words, the reference must teach one of skill in the art how to practice the claimed invention, without undue experimentation. Further, to support an anticipation rejection based on inherency, the Office must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the reference. *See, e.g., Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990). Inherency cannot be established by probabilities or possibilities. *See, e.g., Continental Ca Co. USA, Inc. v. Monsanto Co.* 20 USPQ2d 1746, 1749 (Fed. Cir. 1987).

With these rules in mind, Applicants address the points raised by the Examiner. First and foremost, Domenighini does not disclose, either expressly or inherently, each and every element of the claimed methods. In particular, the claims contain, at least, the following limitations: (1) use of a detoxified LT mutant as parenteral adjuvant; (2) co-administration of the parenteral LT adjuvant with at least one additional selected antigen; and (3) generation of an immune response against the selected antigen. Domenighini does not teach or suggest these claimed elements.

Domenighini does not disclose or suggest methods in which LT-K63 acts as any kind of adjuvant, let alone a parenteral adjuvant as claimed. (*See, also,* Response and del Giudice Declaration, filed October 20, 2000 addressing WO '348 which, like Domenighini, discloses use of LT mutants as antigens only). Rather, the aim in Domenighini was to render LT non-toxic so that it could be safely administered as an antigen in a vaccine against *E. coli*. (*See,* Summary of the Invention). Adjuvanticity (parenteral or otherwise) of LT mutants is nowhere addressed in the cited reference. Indeed, the fact that LT can have its toxicity removed without simultaneously removing its adjuvanticity was, in fact, a surprising finding made *after* Domenighini was filed, as noted in WO 95/17211 (reference AD-1 of IDS, filed May 7, 1998, hereinafter "Rappuoli"):

> "it has now been discovered that, in complete contradiction with the results and conclusions presented in the prior art, the toxic and adjuvant activities of the ADP-ribosylating toxins are separable. An entirely non-

> toxic mutant of such a toxin has been shown to be active as a mucosal adjuvant ... by ensuring that the non-toxic mutant of the invention is stable at the site of delivery it has been demonstrated that the adjuvant effect of CT and/or LT may be maintained while its toxic effects are eliminated." (see, page 5, lines 13-34 of WO 95/17211).

As such, it cannot be fairly said that the claimed invention does not necessarily flow from Domenighini's disclosure. Accordingly, this reference in no way discloses, either expressly or inherently, methods of using LT mutants as parenteral adjuvants.

Similarly, Domenighini also fails to describe and demonstrate another aspect of the pending claims -- methods of inducing an immune response against at least one selected antigen by co-administering an LT mutant parenteral adjuvant. The Examiner maintains that Domenighini's disclosure of administering LT mutants with "bacterial cell wall components" is equivalent to the claimed methods. In support of this argument, the Examiner cites Siadak et al. (U.S. Patent No. 4,834,975) and Golding (U.S. Patent No. 5,824,310) as allegedly establishing that Domenighini et al. inherently discloses "that proteins, polysaccharides and inactive virus particles serve as antigens." (Final Office Action, page 4, emphasis added).

The Examiner's assertions are factually inaccurate and legally improper. The claimed methods are directed to eliciting an immune response against a selected antigen by co-administering a parenteral LT mutant adjuvant with at least one selected antigen. In contrast, the references cited by the Examiner are directed to lippolysacharrides from *Pseudomonas aeruginosa* (Siadak) or *Brucella abortus* (Golding). Simply put, "bacterial cell wall components" are not equivalent to the claimed LT-K63 and LT-R72 parenteral adjuvants. None of the documents cited by the Office disclose that methods of stimulating an immune response against a selected antigen using LT-K63 or LT-R72 as a parenteral adjuvant. Indeed, Office has modified the teachings of Domenighini (directed to vaccines comprising LT-mutants antigens and known adjuvants such as bacterial cell wall components), Siadak and Golding in imposing a rejection of claims directed to

methods directed to enhancing the immunogenicity of a selected antigen by using LT mutants as parenteral adjuvants. This is entirely improper and, accordingly, the rejection should be withdrawn.

The Examiner also cited various references as allegedly establishing that Domenighini inherently discloses the suitability of LT-K63 or LT-R72 as a parenteral adjuvant. In particular, Di Tommasso et al., Partidos et al. and Clements et al. (WO 96/06627) are all cited as establishing the use of LT or LT mutants as mucosal or oral adjuvants. Applicants again remind the Office that inherency cannot be established by probabilities or possibilities. Moreover, although the Office is entitled to rely on additional references in anticipation rejections, these reference must substantiate the inherency of the characteristic at issue. *See, e.g., Continental Can Co, supra.* Thus, in the pending case, any reference cited with Domenighini must substantiate that LT-K63 or LT-R72 are parenteral adjuvants. For the reasons detailed above, Domenighini fails entirely to disclose adjuvant properties of LT mutants. Clements is completely silent as to LT mutants, while Di Tommaso and Partidos are completely silent as to use of LT-K63 as a parenteral adjuvant. Therefore, the references do not substantiate the inherency of the characteristic at issue and, accordingly, the rejection under 35 U.S.C. 102 cannot stand.

In sum, Domenighini does not disclose each and every element of the claimed invention and does not arrange or use the elements in the novel methods set forth in the claims. Therefore, the rejection under 102 should be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 28-30 are rejected under 103(a) as allegedly obvious over Domenighini in view of Rappuoli. Domenighini is cited as above for teaching compositions comprising LT-K63 antigens. Rappuoli is cited for teaching methods of mucosal immunization with mutant LT toxins. (Office Action, paragraph 15). It is alleged that it would have been

obvious to administer Domenighini's composition containing LT-K63 using Rappuoli's methods. (Office Action, paragraph 15).

Applicants traverse the rejection and supporting remarks.

In determining obviousness, the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The references must: teach all the limitations of the claimed invention; provide a reasonable expectation that the claimed methods would be successful; and suggest the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") Furthermore, Section 103 expressly requires that the Office consider the claimed invention "as a whole." (*See, e.g., Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 93 (Fed. Cir. 1986). Thus, for almost 30 years, the courts have consistently held that part of evaluating the invention as a whole includes considering functional language in a claim and defining the invention by what it does, rather than by what it is. (*See, e.g., In re Caldwell,* 138 USPQ 243 (CCPA 1963).

Here, the invention as set forth in claims 28-30 is to methods which use Lt-K63 or LT-R72 mutant as a parenterally-administered adjuvant to enhance the immunogenicity of a selected antigen. Thus, when properly defined by what the invention does, the methods of claim 28-30 includes enhancing the antigenicity of a selected antigen using LT mutants as parenteral adjuvants.

For the reasons detailed above, and those previously presented, Domenighini fails to teach or suggest that LT mutants can function as parenteral adjuvants for a selected

antigen. (*See, also,* Response to Office Action and del Giudice Declaration, filed October 20, 2000.) As such, the primary reference contains no suggestion to arrive at the claimed invention and does not provide the requisite reasonable expectation of success.

The secondary reference, Rappuoli, does not make up for the deficiencies of Domenighini. At best, Rappuoli's disclosure is limited to use of LT mutants as mucosal adjuvants and, like Domenighini, does not teach or suggest use of LT mutants as parenteral (*e.g.,* non-mucosal) adjuvants. Indeed, as noted above, Applicants define "parenteral" to exclude mucosal administration (*see,* page 7, lines 25-26), claims 28-30). At the time of filing, it would have not been expected that mucosal adjuvants would function as parenteral adjuvants and, accordingly, the fact that the claimed LT mutants acted as parenteral adjuvants is a surprising result first demonstrated by Applicants. (See, page 5, lines 13-34 of WO 95/17211, and previous Responses). Thus, the claimed methods are not obvious in view of the combined disclosures of Domenighini and Rappuoli.

The Office has failed to satisfy its burden of establishing a *prima facie* case of obviousness. Therefore, Applicants submit that this rejection is improper and should be withdrawn. In addition, Applicants request, pursuant to 37 C.F.R. § 1.104(d)(2), that the Office support this rejection (for example, the assertion that the teachings of the reference provide a skilled artisan with the requisite expectation of success) with specific data and a supporting affidavit.

II. CONCLUSION

In view of the foregoing, Applicants submit that the claims are now in condition for allowance and requests early notification to that effect.

Please direct all further communications regarding this application to:

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Version Showing Changes Made

19. (Twice Amended) A method for immunizing a vertebrate subject against at least one selected antigen, the method comprising the step of parenterally administering to the vertebrate subject an immunologically effective amount of

a) [an] a parenteral adjuvant comprising a detoxified mutant of an *E. coli* heat-labile toxin (LT) ADP-ribosylating toxin selected from the group consisting of LT-R72 and LT-K63 in combination with a pharmaceutically acceptable vehicle; and

b) at least one selected antigen.

Currently Pending Claims

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a) a parenteral adjuvant comprising a detoxified mutant of an *E. coli* heat-labile toxin (LT) ADP-ribosylating toxin selected from the group consisting of LT-R72 and LT-K63 in combination with a pharmaceutically acceptable vehicle; and

b) at least one selected antigen.

20. Canceled.

21. (Amended) A method according to claim 19 wherein the detoxified mutant comprises one or more amino acid additions, deletions or substitutions in the A subunit of the bacterial toxin.

22. Canceled.

23. (Amended) A method according to claim 19 wherein the detoxified mutant is LT-K63.

24. (Amended) A method according to claim 19 wherein the detoxified mutant is LT-R72.

25. (Amended) A method according to claim 19, wherein the adjuvant and the antigen are administered subcutaneously, transcutaneously or intramuscularly.

26. A method according to claim 19, wherein the pharmaceutically acceptable vehicle is a topical vehicle.

27. A method according to claim 26, wherein the adjuvant and the antigen are administered transcutaneously.

28. A method according to claim 19, wherein the adjuvant is administered to the vertebrate subject prior to administering the selected antigen.

29. A method according to claim 19, wherein the adjuvant is administered to the vertebrate subject subsequent to administering the selected antigen.

30. A method according to claim 19, wherein the antigen is administered to the vertebrate subject concurrent with administering the selected antigen.